PATENT COOPERATION TREA

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

To:
GOUDREAU GAGE DUBUC
& MARTINEAU WALKER
Attn. DUBUC, JEAN H.
800 The Stock Exchange Tower
Victoria Square - P.O. Box 242
MONTREAL, Quebec H4Z 1E9
CANADA

RECEIVED
20 MAR 2000

Applicant's or agent's file reference CG/12326.19	Date of mailing (day/month/year) 16/03/2000
	FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/CA 99/ 00852	International filing date (day/month/year) 15/09/1999
Applicant SIGNALGENE INC. et al.	

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,	Authorized officer Nina Vercio

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped),whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international appplication is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREA

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
CG/12326.19		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/CA 99/ 00852	15/09/1999	15/09/1998
Applicant		
SIGNALGENE INC. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [X] furnished subsequently to this Authority in written form.

   [X] furnished subsequently to this Authority in computer readble form.

   [X] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [X] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. —

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 99/00852

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12Q C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ELHAJI Y ET AL: "The polymorphic CAG repeat of the androgen receptor and female breast cancer" AMERICAN JOURNAL OF HUMAN GENETICS, vol. 61, no. 4 suppl, 28 October 1997 (1997-10-28) - 1 November 1997 (1997-11-01), page A64 XP000884969 see abstract 346 -/--	1-5

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 March 2000	16/03/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,	

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	REBBECK TR ET AL: "Modification of breast cancer risk in BRCA1 mutation carriers by the androgen receptor CAG repeat polymorphism" PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH ANNUAL MEETING, vol. 39, 28 March 1998 (1998-03-28) - 1 April 1998 (1998-04-01), page 366 XP000884978 see abstract 2493	1-5
A	WO 97 17469 A (DANA FARBER CANCER INST INC ;BRIGHAM & WOMENS HOSPITAL (US)) 15 May 1997 (1997-05-15)	1-6
A	HALL RE ET AL: "Regulation of androgen receptor gene expression by steroids and retinoic acid in human breast cancer cells" INTERNATIONAL JOURNAL OF CANCER, vol. 52, no. 5, November 1992 (1992-11), pages 778-84, XP000884982 see abstract	7,8
A	WO 98 05797 A (LAMPARSKI HENRY G ;CALYDON (US); SCHUUR ERIC R (US); YU DE CHAO (U) 12 February 1998 (1998-02-12) page 8, line 4 - line 13	7-9

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/CA 99/00852

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9717469 A	15-05-1997	AU 7722696 A	29-05-1997
WO 9805797 A	12-02-1998	US 5783435 A	21-07-1998
		AU 3972997 A	25-02-1998
		CA 2262438 A	12-02-1998
		EP 0918884 A	02-06-1999

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

DUBUC, JEAN H.
GOUDREAU GAGE DUBUC
& MARTINEAU WALKER
800 The Stock Exchange Tower
Victoria Square - P.O. Box 242
MONTREAL, Quebec H4Z 1E9
CANADA

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	22.12.2000
Applicant's or agent's file reference CG/12326.19	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA99/00852	15/09/1999	15/09/1998

Applicant
SIGNALGENE INC. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel +49 89 2399 - 0 Tx: 523656 epmu d	Digiusto, M

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
CG/12326.19		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA99/00852	15/09/1999	15/09/1998
International Patent Classification (IPC) or national classification and IPC C12Q1/68		
Applicant SIGNALGENE INC. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 6 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
06/04/2000	22.12.2000
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel +49 89 2399 - 0 Tx: 523656 epmu d	Authorized officer Maucher, C

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA99/00852

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1,3-35	as originally filed	
2,2a	with telefax of	11/12/2000

Claims, No.:

1-14	with telefax of	11/12/2000

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:
   - ☐ the drawings, sheets:

5. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)
   see separate sheet

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 1-8 and 13-14 partially with respect to industrial applicability.

because:

   ☒ the said international application, or the said claims Nos. 1-8 and 13-14 partially relate to the following subject matter which does not require an international preliminary examination (*specify*):
   see separate sheet

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination report cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims 1-14
	No:	Claims
Inventive step (IS)	Yes:	Claims 1-14

	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	9-12, 14
	No:	Claims	

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

The arguments filed by the applicant with a letter of 8.12.2000 have been taken into account for establishing said report.

Point I:

The amendments filed with the letter dated 8.12.2000 introduce subject-matter which extends beyond the content of the application as filed, contrary to Article 34(2)(b) PCT. The amendments concerned are the following:

- **claim 8**: non-cancerous cells; no basis for the general term could be found in the originally filed description (p 12, l 19-20 only disclose lymphocytes).
- **claim 9**: "tissue"
- **claim 12**: no basis could be found for the claimed method starting from step b): "assaying a function...as compared to in the absence thereof".
- **page 2a**: "**germline**" mutation; no basis could be found for mutation in this specific cell type. No implicit disclosure is present for the following reasons. A predisposition for breast cancer can be created for instance due to a spontaneous mutation of DNA in other cells than germline cells. The IPEA furthermore believes that such a predisposition can well be diagnosed from somatic cells and does not need to be examined in germline cells only.

Point III:

Claims 1-8, as well as **claim 13** as long as they depend from any one of claims 1-8, relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Point V:

Reference is made to the following documents:

D1: AMERICAN JOURNAL OF HUMAN GENETICS,
vol. 61, no. 4 suppl, 28.10.1997 - 1.11.1997, page A64

D2: WO97/17469

1. Articles 33(2) and (3) PCT

The subject-matter of **claims 1-14** is **novel** (Article 33(2) PCT) in the light of the closest prior art D1, since it is distinguished therefrom in that the androgen receptor is used for determining an individual's predisposition of breast cancer or for screening and selecting an agent which modulates said predisposition.
Furthermore, D1 (l 11 from the bottom) only suggests a correlation of CAG repeat length of AR and breast cancer.

D2 reveals a method of predicting the risk of prostate cancer morbidity and mortality comprising determining the length of the CAG repeat of the androgen receptor gene (abstract, claim 1).
The teaching of said document can not be combined with D1 for the following reasons: a particular marker for a particular cancer (prostate (D1) or breast (D2) cancer) can not be directly transposed to a different type of cancer due to the complexity of the genetic regulation which operates at different hormonal receptors and the intricate interactions of different hormones which can differently affect, in tissue specific fashion, the transactivation of genes they regulate.

Thus, the subject-matter of **claims 1-14** is also **inventive** according to Article 33(3) PCT.

3. Industrial Applicability

For the assessment of the present **claims 1-8**, as well as **claim 13** as long as they depend from any one of claims 1-8, on the question whether they are industrially applicable, no unified criteria exist in the PCT contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture

of a medicament for a new medical treatment.

Point VIII:

1. The vague and imprecise statement "spirit ... of the subject invention" (page 34, line 12) implies that the subject-matter for which protection is sought may be different to that defined in the claims, thereby resulting in lack of clarity of the claims (Article 6 PCT) when used to interpret them (see the Guidelines, C-III, 4.3a). The above statement has not been deleted to remove this defect.

2. The wording of claim 12 is unclear (Article 6 PCT), since it cannot be derived which kind of function ("**a** function") of the allele is assayed.

3. The broad terms "variant", "equivalent" and "mutation" used in claims 1 and 12 are vague and unclear and leave the reader in doubt as to the meaning of the technical features to which they refer, thereby rendering the definition of the subject-matter of said claim unclear (Article 6 PCT).
   Furthermore, the definitions given in the description (page 21, lines 1-17, lines 18-20 and page 22, lines 3-10) do not clarify the terms, since it is not said to what extent these substances are allowed to differ from the androgen receptor gene. The terms "variant" and "mutation" are even so broad that they encompass any nucleic acid molecule, since they are not even limited by the function/s of the androgen receptor gene. Moreover, the definition of the term "equivalent" is as vague since it is silent about how many and which function/s have to remain compared to the androgen receptor gene.

Breast cancers have the same clinical characteristics in older as in younger women. Cancer is usually suspected when changes are noted on mammography or when a breast lesion is seen or felt. Lesions usually can be felt as firm nodules within the breast. Ulcerations may occur, and lesions within or near the nipple may produce discharge. Sometimes breast cancer is discovered only after metastatic lesions cause bone fractures, neurologic changes, hypercalcemia, liver failure, or ascites.

When a tumor is detected by physical examination, bilateral mammograms are normally obtained to rule out occult lesions. Certain radiographic images, such as speckled calcifications or tissue infiltration, suggest cancer, while a cystic appearance suggests a benign process. Even an apparently benign finding on mammogram requires further evaluation. Generally the diagnosis is established by fine needle aspiration. Fine needle aspiration allows collection and cytological examination of cystic fluid and is helpful in planning definitive treatment of breast cancer. Although a positive result on fine needle aspiration is diagnostic, a negative result is usually followed by an open biopsy. Now a day, there is still no specific test for assaying predisposition or resistance to breast cancer.

Since the discovery of the human androgen receptor (AR) gene, mutations in this gene have been associated with Kennedy's disease (spinobulbarmuscolar atrophy), with various degrees of androgen insensitivity and with prostate cancer.

Elhaji et al. (American Journal of Human Genetics, vol. 61, no. 4 suppl, 28.10.1997 – 1.11.1997, page A64) assesses the distribution of CAG-repeat length of the AR in breast cancer tissue to evaluate the possible correlation between the repeat length and the risk of breast cancer. However, Elhaji et al. is concerned with breast cancer tissue *per se* and not with the potential of using AR as a marker for determining the predisposition and prognosis of breast cancer by, for example, screening patients prior to the

development of breast cancer. Indeed, Elhaji et al. suggests that somatic mutations are involved in shifting the distribution of the CAG repeat of the AR gene and thus, that a predisposition and prognosis test could not be carried-out.

Thus, an association between a germline mutation in AR gene and predisposition to breast cancer has yet to be reported.

There thus remains a need to provide a genetic assay for determining the predisposition and/or resistance to breast cancer, development of breast cancer and responsiveness to therapeutic modalities.

While some markers have been identified as genetic determinants for breast cancer and/or as risk factors to develop same (i.e. BRCA1 and BRCA2), there remains a need to identify new markers therefor. More specifically, there remains a need to provide means to determine a

WHAT IS CLAIMED IS:

1. A method of determining an individual's predisposition to breast cancer, development of breast cancer and/or responsiveness to therapy for breast cancer, said method comprising the step of determining a polymorphism at the CAG repeat of the androgen receptor (AR) gene or a DNA variant equivalent, or mutation which shows a linkage disequilibrium therewith, whereby said polymorphism at the AR gene, or marker in linkage disequilibrium therewith enables a prediction of an individual's predisposition to breast cancer, development of breast cancer and/or responsiveness to therapy for breast cancer.

2. The method of claim 1, wherein the androgen receptor genotype is determined by determining the number of CAG repeats within the androgen receptor gene

3. The method of claim 2, which further comprises a step of amplifying a segment of the androgen receptor using polymerase chain reaction.

4. The method of claim 3, wherein a pair of primers derived from a nucleic acid sequence of the androgen receptor gene or flanking said gene is used in the polymerase chain reaction.

5. The method of claim 4, wherein the segment of the androgen receptor gene is amplified using a pair of primers as follows:

5'-TCCAGAATCT GTTCCAGAGC GTGC-3'	SEQ ID NO:1; and
5'-GCTGTGAAGG TTGCTGTTCC TCAT-3'	SEQ ID NO:2.

6. The method according to one of claims 1 to 5, wherein said polymorphism at the AR gene, or marker in linkage disequilibrium therewith, is determined from DNA obtained from said individual.

7. The method of claim 6, wherein said DNA is genomic DNA.

8. The method according to claim 7, wherein said DNA is obtained from non-cancerous cells.

9. The method of claim 8, wherein said cell is obtained from a tissue or blood sample.

10. An assay for screening and selecting an agent which modulates breast cancer predisposition comprising:

a) a recombinant androgen receptor (AR) gene or functional fragment thereof, which comprises a CAG repeat polymorphism in exon 1 thereof, or a marker in linkage disequilibrium therewith; and

b) assaying a function of said androgen receptor;

wherein an allele which modulates said function of said androgen receptor can be selected, and wherein a modulation of a function of said androgen receptor is associated with a modulation of said breast cancer predisposition, whereby short CAG repeats of said AR positively modulate androgen receptor function, while long CAG repeats of said AR negatively modulate Androgen receptor function, thereby leading to breast cancer protection or breast cancer predisposition.

11. An assay for screening and selecting an agent which modulates breast cancer predisposition comprising:

a) an expression vector comprising a promoter operably linked to a reporter gene, said promoter comprising an androgen response

element, said response element affecting the activity of said promoter upon binding thereto of androgen or analog thereof;

b) a cell expressing a chosen allele of an androgen receptor and harboring said vector of a);

c) submitting said cell to at least one agent; and

d) assaying a level of said reporter gene;

whereby an agent which modulates breast cancer predisposition can be selected when the level of said reporter gene is significantly modulated by the presence of said agent through its action through the androgen receptor.

12 A method for screening and selecting an agent which can modulate breast cancer predisposition comprising:

a) selecting a specific allele of the androgen receptor (AR) gene, variant, equivalent, or mutation thereof which shows linkage disequilibrium therewith;

b) assaying a function of said AR allele of a); and

c) selecting an agent which can modulate breast cancer predisposition,

wherein an agent which modulates AR function is selected as an agent capable of modulating breast cancer predisposition when said function is significantly different in the presence of said agent, as compared to in the absence thereof.

13. The method of one of claims 1 to 9, or 12, wherein the shortest alleles or a combination thereof are associated with a protection to breast cancer, and the intermediate to large alleles or a combination of the intermediate and largest alleles are associated with a predisposition to breast cancer.

14. The method of claim 12, wherein said assay is a *cis-trans* assay.